

NCEs and API – Quality by Design

The development and manufacturing of NCE and API is striving for simplifying and shortening timelines, as well as for making more efficient use of chemicals, equipment and facilities. Currently, many pharmaceutical companies are developing green chemistry technologies, as a means to improve production efficiency and reduce costs by incorporating more environmentally friendly methods of green production into the synthesis of APIs and intermediates.

Medicilon is an integrated CRO providing comprehensive one-step new drug R&D for pharmaceutical companies and research institutions around the world. Located in Shanghai Nanhui Industrial Park and Hangzhou biovalley, Medicilon's 180,000 sqm laboratory is equipped with a comprehensive library of instruments and is managed under a high-tech business model and philosophy, aimed at guaranteeing the quality and efficiency of any project undertaken. Bolstered by high-throughput chromatography and mass spectrometry, and advanced processing software, Medicilon sets high standards for compound screening and analysis, optimization of lead compounds, analysis of chemical and physical properties of compounds, and other drug R&D processes.

At Medicilon, chemistry and biology are ingrained in every project. Relying on a rich experience in innovative design and patent strategies that complement state-of-the-art technologies, the company's chemistry team is capable of flexibly applying computer chemistry to assist compound design process. And perfectly equipped to take on multi-dimensional business such as custom synthesis, compound library construction, SAR compound synthesis and screening, compound structure and biological activity optimization.

PROTAC Drug Discovery Technology Platform

At Medicilon, the Medicinal Chemistry Department has established a PROTAC drug discovery platform that contains popular target protein ligands. Medicilon has also set up libraries for high-affinity targeting

protein small molecule (TPSM) and small molecular fragments, libraries for high-affinity ubiquitin ligase small molecule (E3SM) and small molecular fragments, and linker systems that include diversified bi-functional linkers (BF-Linker).

These compound libraries help to quickly and efficiently synthesize a large number of high-activity PROTAC bi-specific small molecules, thus greatly accelerating the process of drug R&D. Also, the company is committed to initiate and complete its PROTAC biological screening and testing platform, and the follow-up development of preclinical stages.

Nucleic Acid Drug R&D Platform

Medicilon's nucleic acid drug R&D platform is an integrated and comprehensive solution that covers drug discovery, CMC, and preclinical research services. Based on a rigorous scientific attitude, an open-minded scientific spirit and advanced equipment, this integrated solution can meet the industry's research and development needs for cutting-edge innovative nucleic acid drugs, and undertake research programs like nucleic acid drug discovery, screening and preclinical research services for pharmaceutical companies and scientific research institutions worldwide.

Medicilon uses medicinal chemistry and computational chemistry to design and synthesize drug-like templates and libraries of compounds meant to increase clients' compound collections. The annual capacity of Medicilon's library production is of more than 100,000 compounds.

Compound Druggability Evaluation

The process of new drug research is lengthy, high-risk, but at the same time very high reward. That's why Medicilon provides druggability evaluation services that are proven to be the most effective in reducing risks.

The so-called druggability refers to the properties of those compounds that have the potential to be developed into a drug, and for which the preliminary pharmacodynamic study and early evaluation of pharmacokinetic properties and safety have already been

performed. It is translational research that helps to build a systematic R&D chain from basic research, preclinical research and clinical efficacy evaluation to new drug manufacturing and clinical application of innovative drugs, to smooth the interaction between the information and the research, between basic medicine science and biology and the R&D of innovative drug and clinical medicine; with the aim of shortening the research and development cycle of innovative drugs from laboratory synthesis to clinical application.

The druggability of a new drug creation includes druglikeness, physicochemical properties, biochemical properties, pharmacokinetics, and toxicity, etc. In the process of new drug development and clinical application, the various parameters of the *in-vivo* process of a compound (absorption, distribution, metabolism, excretion, ADME (toxic pharmacokinetics)) are an important indicator of its druggability.

Preformulation Study

Medicilon preformulation research features both formulation selection and pharmaceutical preparation. As for the low number of active pharmaceutical ingredients or candidate compounds with medicinal properties, the company provides professional preformulation services, exploring valuable information.

Route Selection

Generally, an API involves multiple process routes. The selection of routes will not only affect the possibility of industrial manufacturing, but also the material cost, product quality, and even the environment. Medicilon provides services that include the customization of initial API, as well as the design and determination of synthetic routes.

The company experts also analyse the feasibility of such routes, and the source of synthetic materials, checking if such routes are involved in intellectual property issues, if the cost is acceptable, and if such routes are in compliance with green chemistry principles. Only after that the time comes for conducting route selection, process optimization, quality research, and process verification to ensure project quality.

FULLY INTEGRATED PRECLINICAL DRUG DISCOVERY AND DEVELOPMENT SERVICES

Medicilon is an integrated contract research organization (CRO), providing comprehensive one-stop new drug R&D services from initial idea all the way through the Investigational New Drug (IND) filing phase for global pharmaceutical enterprises and scientific research institutions. Our services span across chemistry, biology, ADME, DMPK and safety evaluation studies. Our preclinical study labs are US FDA and China NMPA GLP and AAALAC accredited. The pilot and production line for small molecule are GMP facility.

- Research Quality focused
- Time efficiency with fast project turnover
- Cost effective
- Easy management with one stop drug discovery platform



FULLY INTEGRATED SERVICES PLATFORM

- Fast assembly of PROTAC molecules and PROTAC screening
- Fast buildings of ADC payloads and ADC screening
- DNA-Encoded Compound Library
- SPR/BiaCore Testing platform
- Protein expression and purification and crystallization biology platform
- Inhalation drug safety R&D platform
- Cellular Immunotherapies R&D platform (RNAi, CAR-T, mRNA vaccine)
- Ophthalmic drug safety R&D platform



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The medicinal chemistry team deeply cross-integrates chemistry and biology into each project, and flexibly uses the powerful expertise of computational chemistry to aid the compound design process. At the same time, Medicilon uses extensively advanced drug discovery technology, including PROTAC targeted protein degradation technology, DEL DNA-encoded small molecule compound library screening technology, ADC antibody drug conjugation technology, etc.

Medicilon's API process route selection and optimization services include: route design and selection; salt form selection, research, and process development of crystal form; salt base selection; crystal form selection; crystal form research (lab-scale testing and kilogram-level); parameter optimization for determined route; statistical and experimental design, based on quality by design (QbD) principles and multivariate data analysis, as well as quality research on API and intermediates, development and verification of analytical methods and technology transfer and process verification.

With the evaluation of the selected route' technological feasibility, usability of equipment, availability of raw materials and reagents, steps of reaction, patent protection, and environmental impact, Medicilon helps clients develop reliable, low-cost, safe, and environment-friendly mass-production API process routes for the selection of both emergency routes in the early stages of drug development, as well as the economic routes for formal drug development.

Technology Transfers

By continuously optimizing processes to obtain a mature and easy-to-industrialize process route, Medicilon sets up a database for key process parameters. According to the characteristics of process routes, a complete impurity profile of starting materials, intermediates, and raw materials is determined, so that the prepared API can meet generic drug requirements, thus enabling industrial production.

Early Pharmacokinetics

Discovery DMPK is an essential part of drug discovery, as it is conducive to the evaluation of compound properties in the early stage, playing an important role in R&D efficiency improvement and risk reduction in later stages. Medicilon is one of the first CRO companies in China to offer discovery DMPK services. The company relies on an experienced pharmacokinetic research team, as well as on the advanced platform

that provides fast and reliable early DMPK services for clients.

Why is Early DMPK Important?

In 1991, up to 40% of failures in the clinical phase of new drug development were associated with drug DMPK properties; in 2000, the likelihood of late failure was dramatically reduced to less than 10% as major pharmaceutical companies shifted to early DMPK studies. Early pharmacokinetic testing allows for a low-cost, short-term risk-benefit assessment of new drug development projects, guiding the processes from the optimization of lead compounds to the determination of preclinical drug candidate.

With 18+ years of accumulated experience, completing preclinical DMPK filing studies for about 20 new drugs each year and *in vivo* PK screening of >2000 compounds per year, Medicilon represents the one-stop-shop for PK/PD, antibody/ADC preclinical DMPK services and technical service solution for isotope drug metabolism research.

APIs

Currently, Medicilon features a cGMP-based API production line based on IND. From preclinical laboratory-scale testing and process development to commercialized production, Medicilon is meeting the industry needs throughout the comprehensive supply chain, including R&D, purchase and production. From the mg- and g-level to kg level, Medicilon's processes allow flexible adjustments to fit in client innovative process R&D and scale production. From QBD-oriented process design to process R&D in laboratories, commercialized production to data-based filings, the analysis and quality inspection teams deliver professional services and comprehensive analytical research, including method development and verification, process verification, impurity identification and separation, API and intermediates research, and API stability tests.

With years of experience and the construction of laboratories, Medicilon Process Department can not only perform R&D, testing and stability studies of generic drugs for customers, but also R&D, production, testing and stability studies of innovative drugs in clinical phase I and phase II, gradually developing from process R&D to industrial commercial production and transforming from CRO to CDMO.

Chemical Drug Development

Medicilon offers the one-stop shop integrated

chemical drug R&D services including customized synthesis, medicinal chemistry, focused library preparation and process chemistry. Either in FTE or integrated project team arrangement, the company's chemistry team is committed to helping clients discover novel and potent chemical series. Medicilon contribution has led to numerous preclinical and clinical candidates, also providing scale-up service to timely deliver kilograms of high-quality compounds.

With the rapid development of the global pharmaceutical market and the division of labour in the pharmaceutical industry, the chain is becoming more and more refined, making specialised outsourcing in the pharmaceutical industry an important strategic choice for pharmaceutical companies. In the early stages of new drug development, FTE (Full-time equivalent) is often used by drug discovery companies to synthesize the required structural fragments and/or potential candidate compounds to accelerate the drug screening process.

As Medicilon offers a full range of chemistry research services covering all phases of any project requirements, clients can choose between the FFS (project-based payment) or FTE (full-time equivalent service) models.



Nadine Su

Nadine is looking after a business alliance with research and business partners for Medicilon UK and European markets. Nadine Su has 15 years of experience in business development and project management in the pharmaceutical and healthcare industries. She successfully led and managed the novel drug research project and formed an international partnership to achieve over \$20M in licensing deals. She has rich experience managing and developing novel technology drug discovery programs from early research to the clinical stage. Her leadership has contributed to the company achieving the "final list of the business award" twice in the Cambridge Business Award competition. Nadine has been educated in China and UK with a master's degree in International Business.

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